(14)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 285/12, 211/12, C07C 323/14, 255/50, 317/10	A1	(11) International Publication Number: WO 98/56779
		(43) International Publication Date: 17 December 1998 (17.12.98)

(21) International Application Number: PCT/US98/12304

(22) International Filing Date: 12 June 1998 (12.06.98)

(30) Priority Data:
60/050,903 13 June 1997 (13.06.97) US

(71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): DAINES, Robert, A. [US/US]; 2587 Cold Spring Road, Lansdale, PA 19466 (US). CHAMBERS, Pamela, A. [US/US]; 423 Jean Drive, King of Prussia, PA 19406 (US).

(74) Agents: STEIN–FERNANDEZ, Nora et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406–0939 (US).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 4–SULFINYL BENZAMIDES AS CALCITONIN GENE–RELATED PEPTIDE RECEPTOR ANTAGONISTS

(57) Abstract

This invention relates to 4–sulfinyl benzamide compounds which are ligands, in particular, antagonists, of the Calcitonin Gene–Related Peptide ("CGRP") receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CGRP, including, but not limited to, headaches, especially migraines; non–insulin dependent diabetes mellitus; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, by the use of 4–sulfinyl benzamide CGRP receptor antagonists.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

4-SULFINYL BENZAMIDES AS CALCITONIN GENE-RELATED PEPTIDE RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to 4-sulfinyl benzamide compounds which are ligands, in particular, antagonists, of the Calcitonin Gene-Related Peptide (hereinafter "CGRP") receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CGRP, including, but not limited to, headaches, especially migraines; non-insulin dependent diabetes mellitus ("NIDDM"); neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, preferably humans, by the use of CGRP receptor ligands, in particular, 4-sulfinyl benzamide antagonists, thereof.

BACKGROUND OF THE INVENTION

CGRP is a 37 amino acid polypeptide that is stored and released from nerve terminals in both the central nervous system and the peripheral nervous system. (Goodman et al., *Life Sci.*, Vol. 38, pp. 2169-2172 (1986)). CGRP has been detected in nerves innervating the heart, peripheral and cerebral blood vessels, and kidneys by immunohistochemical and radioimmunoassay methods. (Yamamoto et al., *Prog. Neurobiol.*, Vol. 33, pp. 335-386 (1989)). CGRP has been shown to mediate its biological response by binding to specific cell surface receptors that have been identified in a variety of tissues. Evidence from biochemical studies suggest that CGRP receptors belong to the family of G-protein coupled receptors. The widespread distribution of CGRP receptors on muscle, glandular, epithelial and neuronal cells is consistent with its wide range of biological actions, including pain transmission (Collin et al., *Pain*, Vol. 54, p. 20 (1993); and *J. Neurosci.*, Vol. 16, No. 7, pp. 2342-2351 (1996)); peripheral and cerebral vasodilation (Brain et al., *Nature*, Vol. 313, pp. 54-56 (1985)); cardiac acceleration (Sigrist et al., *Endocrinology*, Vol. 119, pp. 381-389 (1986)); regulation of calcium metabolism (Grunditz et al., *Endocrinology*, Vol. 119, pp. 2313-2324 (1986)); reduction of intestinal motility (Fargeas et al., *Peptides*, Vol. 6, pp. 1167-1171 (1985)); regulation of glucose metabolism, e.g., reduction of insulin secretion and insulin sensitivity, (Hermansen et al., *Peptides*, Vol. 27, pp. 149-157 (1990); and Molina et al., *Diabetes*, Vol. 39, pp. 260-265 (1990)); reduction of appetite and reduction of growth hormone increase (Tannenbaum et al., *Endocrinology*, Vol. 116, pp.

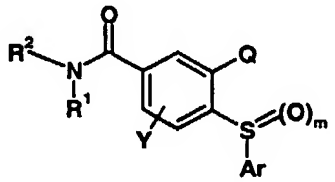
2685-2687 (1985)); reduction of inflammation of the skin, for example in allergic contact dermatitis (Gutwald et al., *J. Invest. Derm.*, Vol. 96, pp. 695-698 (1991)) and other inflammatory skin conditions (Buckley et al., *Neuroscience*, Vol. 48, pp. 963-968 (1992); and Escott et al., *Br. J. Pharmacol.*, Vol. 110, pp. 772-776 (1993)).

Since CGRP has a number of effects on the cardiovascular, central nervous, gastrointestinal, respiratory, and endocrine systems, it has now been discovered that limited and selective inhibition of CGRP receptor mechanisms represents a novel preventative and therapeutic approach to the treatment of a broad variety of disease states that are mediated by CGRP. In particular, the development of an active CGRP receptor antagonist would be expected to be useful in the treatment of a variety of disease states that are mediated by CGRP including, but not limited to, headaches, especially migraines; NIDDM; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, preferably humans ("CGRP-mediated diseases").

Surprisingly, it has now been discovered that a class of non-peptide compounds, in particular 4-sulfinyl benzamides of formula (I) function as CGRP receptor antagonists, and therefore, have utility in the treatment of disease states wherein inhibition of CGRP receptor mechanisms is indicated for prevention or therapeutic treatment thereof.

SUMMARY OF THE INVENTION

In one aspect, the present invention is to a genus of novel compounds of formula (I), or pharmaceutically active salts thereof, said compounds which are also useful in treating the above-mentioned CGRP-mediated disease states:



Formula (I)

wherein:

Q is NO_2 or NH_2;

Y is hydrogen, halo, CF_3, alkyl, alkoxy, NO_2, cyano;

R^1 is phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl;

R^2 is H, methyl, C_{2-4} alkyl, CH_2-A-$CONR^3R^4$, CH_2-A-CO_2R^5, CH_2-A-COR^5, CH_2-A-$SO_2NR^3R^4$, CH_2-A-$N(R^3)SO_2R^5$, CH_2-A-$N(R^3)COR^5$, CH_2-A-$N(R^3)CO_2R^6$, CH_2-A-$N(R^3)C(O)NR^3R^4$, CH_2-A-$N(R^3)C(O)NR^3SO_2R^5$, or CH_2-A-$OC(O)NR^3R^4$;

A is $(CH_2)_n$ where n is 0-6, or C_6H_4;

R^3 and R^4 independently are H, C_{1-6} alkyl, or C_{1-4} alkylphenyl, or R^3 and R^4, together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring such as piperidine, piperazine, or morpholine;

R^5 is methyl, trifluoromethyl, C_{2-6} alkyl (including branched alkyls), phenyl, or heteroaryl;

R^6 is tert-butyl, CH_2-phenyl, or CH_2-pyridinyl;

m is 0, 1 or 2; and

Ar is phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl.

In another aspect, the present invention is to a method of treating CGRP mediated diseases, all in mammals, preferably humans, comprising administering to such mammal in need thereof, an effective amount of a 4-sulfinyl benzamide compound of formula (I), or a pharmaceutically active salt thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically active salt thereof, and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating CGRP-mediated disease states, including, but not limited to headaches, especially migraines; NIDDM; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, preferably humans.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that 4-sulfinyl benzamide compounds of formula (I) are CGRP receptor ligands, in particular, antagonists thereof. It has also now been discovered that selective inhibition of CGRP receptor mechanisms by treatment with the receptor ligands of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of CGRP-mediated disease states.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited

thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n- propoxy, isopropoxy, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heteroring" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 5-, 6-, or 7-membered ring system which contains one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, and the like.

The terms "aryl" or "heteroaryl" are used herein at all occurrences to mean substituted and unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems and heteroaryl moieties, which may include, but are not limited to, heteroatoms selected from O, N, or S. Representative examples include, but are not limited to, phenyl, benzyl, naphthyl, pyridyl, quinolinyl, thiazinyl, furanyl, imidazolidine, pyrazolidine, thiazole, immidazole, thiadiazole, triazole, benzothiazole, and the like.

The term "CGRP mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by Calcitonin Gene-Related Peptide.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloric, sulfate, phosphate, diphosphate, hydrobromide and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate and stearate. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with

pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic (particularly when oxidation of the sulfide results in a racemic mixture of sulfoxides) and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention. Also within the scope of this invention are the corresponding sulfides of the examples cited herein which may serve as prodrug forms of the active sulfoxides.

For the compounds of formula (I) various embodiments are as follows.

Q is suitably NO_2 or NH_2. Q is preferably NO_2.

Y is suitably hydrogen, halo, CF_3, alkyl, alkoxy, NO_2, cyano.

R^1 is suitably phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl. R_1 is preferably substituted phenyl. As used herein for R_1, the term "substituted" means that the phenyl or heteroaryl moiety is substituted with one or more, up to three, of the following functional groups, C_{1-6} alkyl, halo, alkoxy, CF_3, CN, or NO_2. Preferably, the phenyl or heteroaryl moiety is substituted by C_{1-4} alkyl. Most preferably, the phenyl or heteroaryl moiety is substituted by C_{1-4} alkyl, in the ortho position.

R^2 is suitably H, methyl, C_{2-4} alkyl, CH_2-A-$CONR^3R^4$, CH_2-A-CO_2R^5, CH_2-A-COR^5, CH_2-A-$SO_2NR^3R^4$, CH_2-A-$N(R^3)SO_2R^5$, CH_2-A-$N(R^3)COR^5$, CH_2-A-$N(R^3)CO_2R^6$, CH_2-A-$N(R^3)C(O)NR^3R^4$, CH_2-A-$N(R^3)C(O)NR^3SO_2R^5$, or CH_2-A-$OC(O)NR^3R^4$.

A is suitably $(CH_2)_n$ where n is 0-6, or C_6H_4. Preferably, A is $(CH_2)_n$, wherein n is 2-4.

R^3 and R^4 independently are suitably H, C_{1-6} alkyl, or C_{1-4} alkylphenyl, or R^3 and R^4, together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring such as piperidine, piperazine, or morpholine.

R^5 is suitably methyl, trifluoromethyl, C_{2-6} alkyl (including branched alkyls), phenyl, or heteroaryl.

R^6 is suitably tert-butyl, CH_2-phenyl, or CH_2-pyridinyl. Preferably, R^6 is tert-butyl or CH_2-phenyl.

Variable m is suitably 0, 1, or 2, preferably m is 1.

Ar is phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl. Preferably, Ar is heteroaryl. As used herein for Ar, the term "substituted" means that the phenyl or heteroaryl moiety is substituted with one or more, up to three, of

the following functional groups, C_{1-6} alkyl, halo, alkoxy, carboxymethyl, CF_3, CN, NO_2, amino, or phenyl. It will be understood that the optional substituent(s) may be in an ortho, meta or para position on the phenyl or heteroaryl ring.

Among the preferred compounds of the invention are the following compounds:

(±)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;

(+)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;

(-)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;

(±)-4-[(4-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;

(±)-N-methyl-N-(2-methylphenyl)-4-[(1-oxido-2-pyridinyl)sulfinyl]-3-nitrobenzamide;

(±)-N-methyl-N-(2-methylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide;

(±)-N-methyl-N-(2-methylphenyl)-4-[(5-methyl-1, 3, 4-thiadiazol-2-yl)sulfinyl]-3-nitrobenzamide; and

N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an amount sufficient to treat headaches, especially migraines; NIDDM; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the

carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CGRP mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating CGRP-mediated diseases with an antagonist as depicted in formula (I). By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for a CGRP-mediated disease state, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

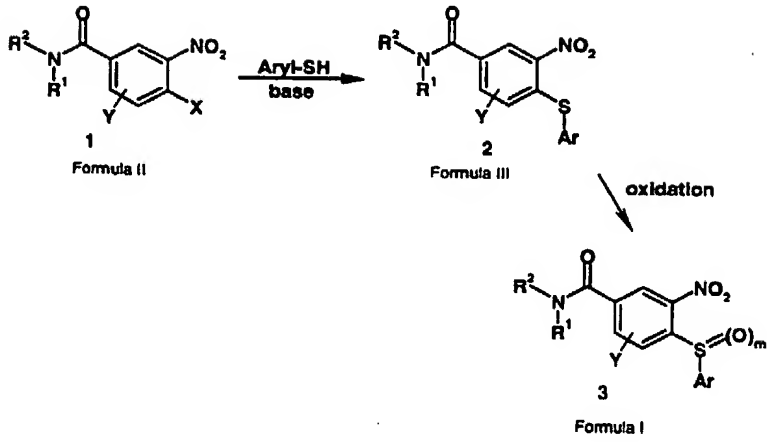
The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods of Preparation

Generally, the compounds of the invention may be prepared by the following reaction sequence:

Scheme 1



Scheme 1 illustrates a process in which a 3-nitrobenzamide of formula (II) (**1-Scheme 1**), containing a suitable leaving group **X** which is a halogen, preferably, fluorine, or a nitro group, is treated with an aryl thiol in the presence of a base. This process produces the sulfide of formula (III) (**2-Scheme 1**) which is then converted to the desired sulfoxide of formula (I) (**3-Scheme 1**) by using an appropriate oxidizing agent. R^1 and R^2 are as defined above. Specific examples of this process are given in Schemes 2 and 3.

This reaction may be accomplished in any of a variety of reaction inert solvents by mixing approximately equimolar amounts of a compound of Formula II and the aryl thiol in the presence of a base at or below room temperature. The proper choice of reaction variables is within the skill of the art. DMF is the preferred solvent. Suitable bases are potassium carbonate, DBU, and the like. In general, the reaction is allowed to proceed for about 2 hours to about 24 hours at which time the reaction is substantially complete. The completeness of a particular reaction may be measured by known techniques such as thin layer chromatography. The reaction mixture is then treated with sodium bicarbonate.

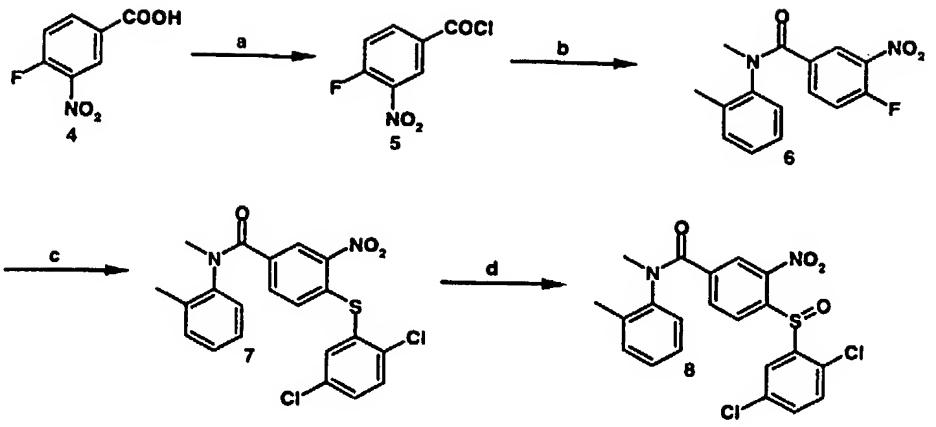
The products of the reaction are isolated and purified by standard procedures. For example, the reaction mixture may be concentrated by evaporating the solvent and the residue may be partitioned between water and a convenient nonwater-miscible organic solvent such as ether, ethyl acetate, and the like. The solvent may then be evaporated and the residue chromatographed, for example, on silica gel. Choice of the proper chromatography solvent is within the skill of the art. After, or instead of, chromatography, the product may be recrystallized.

Acid addition salts may be prepared using standard procedures. For example, a hydrochloride salt may be prepared by dissolving the free base in a convenient solvent and treating this solution with a solution of hydrogen chloride dissolved in the solvent of choice. The acid addition salts may be reconverted to the respective free base by treatment with a dilute solution of sodium hydroxide or potassium carbonate, for example.

The compounds of formula (I) are prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Scheme 2 illustrates the preparation of the compound described in Example 1 (i.e., **8-Scheme 2**). Commercially available 4-fluoro-3-nitrobenzoic acid (**4-Scheme 2**) is converted to the acid chloride **5-Scheme 2** using a suitable agent such as, but not limited to, oxalyl chloride or thionyl chloride. In the case of oxalyl chloride, this reaction may be carried out using methylene chloride as a solvent with the addition of a catalytic amount of dimethylformamide. This acid chloride is next coupled to the desired aniline portion via standard acylation conditions (e.g., triethylamine, methylene chloride, 0 °C). Alternatively, the acid **4-Scheme 2** may be directly coupled to the aniline using standard peptide coupling reagents (e.g., DCC or BOP, HOBT, N-methylmorpholine). Using these methods, the desired benzamide **6-Scheme 2** may be obtained. In this example, N-methyl-o-toluidine is used to illustrate the process. Reaction of **6-Scheme 2** with an aryl thiol (aryl mercaptan) such as 2, 5-dichlorothiophenol in the presence of a base such as powdered potassium carbonate in an aprotic solvent such as dimethylformamide, produces the sulfide-containing benzamide **7-Scheme 2**. Conversion of the sulfide **7-Scheme 2** to the sulfoxide **8-Scheme 2** is then accomplished by treatment with a suitable oxidizing agent. In this example, 3-chloroperoxybenzoic acid (mCPBA) was used, however, other agents well known in the art could have been employed.

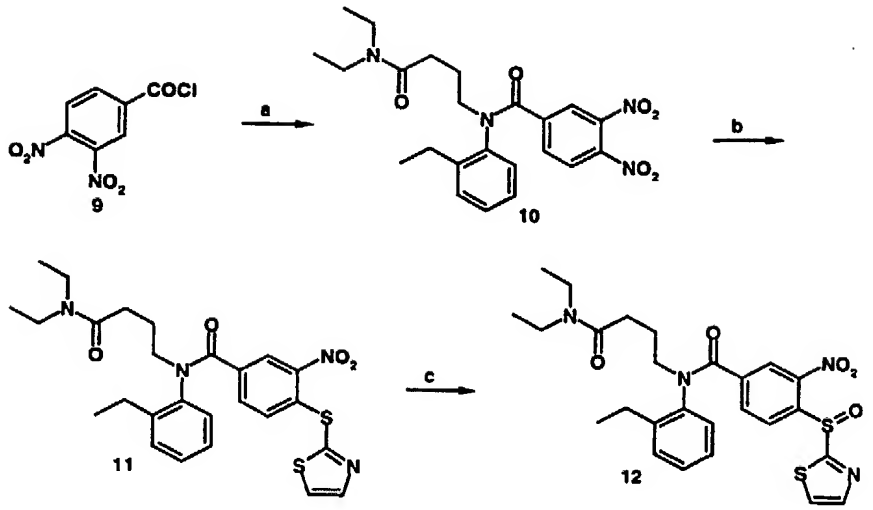
Scheme 2



Reagents: (a) oxalyl chloride, CH_2Cl_2, cat. DMF, rt.; (b) N-methyl-o-toluidine, triethylamine, CH_2Cl_2, 0 °C; (c) 2, 5-dichlorothiophenol, K_2CO_3, DMF, rt.; (d) mCPBA, CH_2Cl_2, 0 °C.

Scheme 3 illustrates the case in which a 3, 4-dinitrobenzamide (i.e., wherein X of formula (II) is NO_2) is utilized as a starting material (Example 31). Acid chloride **9-Scheme 3** may be prepared using methods outlined above. Acylation as previously described using **9-Scheme 3** and an aniline provides the 3, 4-dinitrobenzamide **10-Scheme 3**. Conversion of **10-Scheme 3** to the desired sulfide is performed as described in Scheme 2 (aryl thiol, K_2CO_3, DMF). In this example 2-mercaptothiazole was employed as the aryl thiol to produce the sulfide **11-Scheme 3**. Oxidation as before (mCPBA) yields the target sulfoxide **12-Scheme 3**.

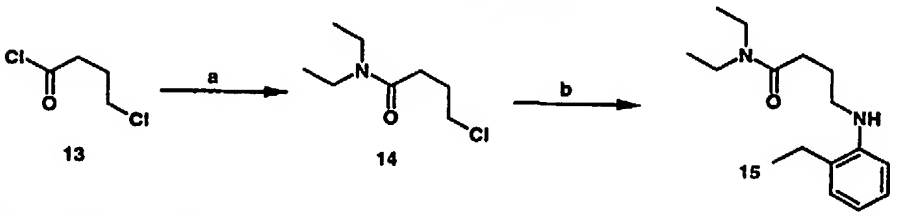
Scheme 3



Reagents: a) **15**, triethylamine, CH_2Cl_2, 0 °C; b) 2-mercaptothiazole, K_2CO_3, DMF, rt.; c) mCPBA, CH_2Cl_2, 0 °C.

Preparation of the aniline **15-Scheme 4** used in the preparation of Example 31 (Scheme 3) is shown in Scheme 4. This procedure is quite general and may be used to prepare a wide range of anilines of which compound **15-Scheme 4** is just one example. In this particular example, 4-chlorobutyryl chloride (**13-Scheme 4**) is reacted with diethylamine to provide the diethylamide **14-Scheme 4**. Alkylation of 2-ethylaniline using **14-Scheme 4** as the alkylating agent then provides **15-Scheme 4**. Aniline **15-Scheme 4** is then used as illustrated in Scheme 3.

Scheme 4



Reagents: a) diethylamine, triethylamine, CH_2Cl_2, 0 °C; b) 2-ethylaniline, triethylamine, DMF, 100 °C.

EXAMPLES

Example 1. Preparation of (±)-4-[(2, 5-dichlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

a) 4-Fluoro-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

To a stirred solution of 4-fluoro-3-nitrobenzoic acid (3.70 g, 20.0 mmol) in methylene chloride (50 mL) at 0° C was added oxalyl chloride (4.0 mL, 46.0 mmol), followed by dimethylformamide (1uL). The reaction was stirred at ambient temperature for 1.5 h. The reaction solution was evaporated to dryness under reduced pressure. The crude acid chloride was redissolved in methylene chloride (40 mL) and added at 0°C to a stirred solution of N-methyl-o-toluidine (2.24 mL, 20.0 mL) and triethylamine (2.78 mL, 20.0 mL) in methylene chloride (20 mL). The reaction was stirred at ambient temperature for 1h. After standing for 18h, the reaction was treated with saturated sodium bicarbonate (60mL). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to yield a tan oil. Crystallization from diethyl ether gave the title compound as a light beige solid (4.56g, 79%). MS(ES) m/e 289.1 $[M+H]^+$.

b) (±)-4-[(2, 5-Dichlorophenyl)thio]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

To a stirred solution of the compound of Example 1(a) (72mg, 0.25 mmol) in dimethylformamide (1.5 mL) was added 2, 5-dichlorothiophenol (49.2 mg, 0.275 mmol) and anhydrous powdered potassium carbonate (38.0 mg, 0.275 mmol). The reaction was stirred at ambient temperature. After 18 h, the reaction was treated with saturated sodium bicarbonate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to afford a yellow solid. MS(ES) m/e 447.1 $[M+H]^+$, 469.1 $[M+Na]^+$.

c) (±)-4-[(2, 5-Dichlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

To a stirred solution of the compound of Example 1(b) (111.5 mg, 0.25 mmol) in methylene chloride (5 mL) at 0° C, was added 50% m-chloroperoxybenzoic acid (88.6 mg, 0.258 mmol). After 40 min, the reaction was treated with saturated sodium bicarbonate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to afford a yellow oil. Flash chromatography (silica gel, 2:1 hexane:ethyl acetate) gave a pale yellow oil. Crystallization from diethyl ether yielded the title compound (59.4 mg, 51%). MS(ES) m/e 463.2 $[M+H]^+$, 485.0 $[M+Na]^+$; mp 168-171°C.

The following compounds were purified either by flash column chromatography (silica gel, hexane/ethyl acetate), or by crystallization (ethyl acetate or diethyl ether).

Example 2. Preparation of (±)-N-methyl-N-(2-methylphenyl)-3-nitro-4-(phenylsulfinyl)benzamide

Prepared according to Example 1 by substituting thiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 395.2 $[M+H]^+$, 417.2 $[M+Na]^+$.

Example 3. Preparation of (±)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-chlorothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 429.1 $[M+H]^+$, 451.1 $[M+Na]^+$.

Example 4 and 5. Preparation of (+)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide and (-)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

The racemic compound of Example 3 (50 mg) was separated into the title enantiomeric forms by preparative LC using Daicel Chiralcel® OD; 25 cm x 21.2 mm; ethanol, 100%; 8.0 mL/min; UV detection at 254 nm yielding the (+) sulfoxide enantiomer (19.9 mg) $[\alpha]_D$ +10.9° (c 0.9, $CHCl_3$); HPLC t_R 10.27 min (Daicel Chiralcel® OD; 25 cm x 4.6 mm; ethanol:hexane, 60:40, 1.0 mL/min; UV detection at 215 nm)and the (–) sulfoxide enantiomer (18.1 mg) $[\alpha]_D$ −11.6 (c 0.80, $CHCl_3$); HPLC t_R 20.25 min (Daicel Chiralcel® OD; 25 cm x 4.6 mm; ethanol:hexane, 60:40, 1.0 mL/min; UV detection at 215 nm).

Example 6. Preparation of (±)-4-[(3-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 3-chlorothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 429.1 $[M+H]^+$, 451.1 $[M+Na]^+$.

Example 7. Preparation of (±)-4-[(4-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 4-chlorothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 429.1 $[M+H]^+$, 451.1 $[M+Na]^+$.

Example 8. Preparation of (±)-4-[(2, 4-dichlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2, 4-dichlorothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 463.2 $[M+H]^+$, 485.0 $[M+Na]^+$.

Example 9. Preparation of (±)-4-[(3, 4-dichlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 3, 4-dichlorothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 463.0 $[M+H]^+$, 484.9 $[M+Na]^+$.

Example 10. Preparation of (±)-4-[(2-bromophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-bromothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 472.8 $[M+H]^+$.

Example 11. Preparation of (±)-4-[(4-fluorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 4-fluorothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 413.0 $[M+H]^+$.

Example 12. Preparation of (±)-4-[(2-isopropylphenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-isopropylthiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 437.2 $[M+H]^+$.

Example 13. Preparation of (±)-4-[(2-methylphenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-methylthiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 406.9 $[M-H]^-$, 431.3 $[M+Na]^+$.

Example 14. Preparation of (±)-4-[(2-methoxyphenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-methoxythiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 425.2 $[M+H]^+$, 447.3 $[M+Na]^+$.

Example 15. Preparation of (±)-methyl 2-[[4-[[methyl-(2-methylphenyl)amino]carbonyl]-3-nitrophenyl]sulfinyl]benzoate

Prepared according to Example 1 by substituting methyl thiosalicylate for 2, 5-dichlorothiophenol. MS(ES) m/e 453.3 $[M+H]^+$, 475.2 $[M+Na]^+$.

Example 16. Preparation of (±)-4-[(4-bromophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 4-bromothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 473.0 $[M+H]^+$.

Example 17. Preparation of (±)-N-methyl-N-(2-methylphenyl)-3-nitro-4-(2-pyrimidinylsulfinyl)benzamide

Prepared according to Example 1 by substituting 2-mercaptopyrimidine for 2, 5-dichlorothiophenol. MS(ES) m/e 397.2 $[M+H]^+$, 419.2 $[M+Na]^+$.

Example 18. Preparation of (±)-N-methyl-N-(2-methylphenyl)-4-[(4-methyl-2-pyrimidinyl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 4-methyl-2-mercaptopyrimidine for 2, 5-dichlorothiophenol. MS(ES) m/e 411.1 $[M+H]^+$, 433.0 $[M+Na]^+$.

Example 19. Preparation of (±)-N-methyl-N-(2-methylphenyl)-4-[(1-methyl-2-imidazolyl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-mercapto-1-methylimidazole for 2, 5-dichlorothiophenol. MS(ES) m/e 399.3 $[M+H]^+$.

Example 20. Preparation of (±)-4-[(2-aminophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-aminothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 410.3 $[M+H]^+$.

Example 21. Preparation of (±)-4-[(3-aminophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 3-aminothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 410.1 $[M+H]^+$.

Example 22. Preparation of (±)-4-[(3-methoxyphenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 3-methoxythiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 425.0 $[M+H]^+$.

Example 23. Preparation of (±)-N-methyl-N-(2-methylphenyl)-4-[(1-oxido-2-pyridinyl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-mercaptopyridine-N-oxide for 2, 5-dichlorothiophenol. MS(ES) m/e 412.1 $[M+H]^+$, 434.1 $[M+Na]^+$.

Example 24. Preparation of (±)-4-[(4-aminophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting 4-aminothiophenol for 2, 5-dichlorothiophenol. MS(ES) m/e 410.1 $[M+H]^+$.

Example 25. Preparation of (±)-4-[(5-amino-1H-1, 2, 4,-triazol-3-yl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide

Prepared according to Example 1 by substituting by 3-amino-5-mercapto-1, 2, 4-triazole for 2, 5-dichlorothiophenol. MS(ES) m/e 401.1 $[M+H]^+$, 399.1 $[M-H]^-$.

Example 26. Preparation of (±)-N-methyl-N-(2-methylphenyl)-4-[(4-phenyl-2-thiazolyl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-mercapto-4-phenylthiazole for 2, 5-dichlorothiophenol. MS(ES) m/e 478.0 $[M+H]^+$.

Example 27. Preparation of (±)-N-methyl-N-(2-methylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide

Prepared according to Example 1 by substituting 2-mercaptothiazole for 2, 5-dichlorothiophenol. MS(ES) m/e 402.1 $[M+H]^+$.

Example 28. Preparation of (±)-N-methyl-N-(2-methylphenyl)-4-[(2-naphthyl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-mercaptonaphthalene for 2, 5-dichlorothiophenol. MS(ES) m/e 445.1 $[M+H]^+$.

Example 29. Preparation of (±)-N-methyl-N-(2-methylphenyl)-4-[(5-methyl-1, 3, 4-thiadiazol-2-yl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-mercapto-5-methylthiadiazole for 2, 5-dichlorothiophenol. MS(ES) m/e 417.2 $[M+H]^+$.

Example 30. Preparation of (±)-N-(2-n-butylphenyl)-4-[(4-chlorophenyl)sulfinyl]-3-nitrobenzamide

Prepared according to Example 1 by substituting 2-n-butylaniline for N-methyl-o-toluidine and 4-chlorothiophenol for 2, 5-dichlorothiophenol. MS(ES) 457.0 $[M+H]^+$.

Example 31. Preparation of N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide

a) N-[3-[(Diethylamino)carbonyl]propyl]-2-ethylaniline

A solution of diethylamine (1.4 mL, 13.7 mmol) in methylene chloride (20mL) was cooled to 0 °C and treated with triethylamine (2.1 mL, 15 mmol) and 4-chlorobutyryl chloride (1.7 mL, 15 mmol). The resulting mixture was gradually warmed to room temperature and stirred for 20 h. The reaction was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was pump-dried overnight and used directly in the following step.

A solution of 2-ethylaniline (250 mg, 2.06 mmol) in N, N-dimethylformamide (6 mL) was treated with the crude chloride prepared above (550 mg, 3.1 mmol), triethylamine (0.48 mL, 3.4 mmol), and tetra-*n*-butylammonium iodide (74 mg, 0.2 mmol). The resulting mixture was stirred at 90 °C for 20 hours. The reaction was diluted with ethyl acetate and washed with water, 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 20:10:70 and 30:10:60 ethyl acetate-methylene chloride-hexane) to afford the title compound (215 mg, 40%) as a viscous light brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, 1H), 7.06 (d, 1H), 6.69 (t, 1H), 6.61 (d, 1H), 4.10 (bs, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 3.21 (t, 2H), 2.62-2.40 (m, 4H), 2.13-2.02 (m, 2H), 1.25 (t, 3H), 1.08-1.24 (m, 6H).

b) N-[3-[(Diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

A solution of the compound of Example 31(a) (211 mg, 0.807 mmol) in methylene chloride (2.2 mL) was cooled to 0 °C and treated with triethylamine (0.12 mL, 0.85 mmol) and 3, 4-dinitrobenzoyl chloride (195 mg, 0.85 mmol). The resulting mixture was gradually warmed to room temperature and stirred for 20 h.

The reaction was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 30:10:60, 40:10:50, and 50:10:40 ethyl acetate-methylene chloride-hexane) to afford the title compound (242 mg, 66%) as a golden yellow oil. MS (ES) m/e 457.1 $[M+H]^+$.

c) N-[3[(Diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3-nitro-4-(2-thiazolylthio)benzamide

A solution of the compound of Example 31 (b) (50.5 mg, 0.11 mmol) in acetonitrile (1 mL) was treated with 2-mercaptothiazole (19 mg, 0.165 mmol) and potassium carbonate (23 mg, 0.165 mmol). The resulting mixture was stirred at room temperature for 20 h. The reaction was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound (50 mg, 86%) as a viscous golden yellow oil. MS (ES) m/e 527.2 $[M+H]^+$.

d) N-[3-[(Diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide

A solution of the compound of Example 31 (c) (39 mg, 0.074 mmol) in methylene chloride (1.5 mL) was cooled to 0 °C and treated with 3-chloroperoxybenzoic acid (26.4 mg, 0.076 mmol). The resulting mixture was gradually warmed to room temperature and stirred for 1 h. The reaction was diluted with methylene chloride and washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 1% and 3% methanol in methylene chloride) to afford the title compound (32 mg, 81%) as a viscous light golden yellow oil. MS (ES) m/e 543.1 $[M+H]^+$.

Example 32. Preparation of (±)-3-amino-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)benzamide

A mixture of 4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide (21 mg, 0.049 mmol), obtained as described in Example 3, and anhydrous stannous chloride (48 mg, 0.253 mmol) in absolute ethanol was heated at 65-70° under argon for 30 minutes. The reaction was cooled to room temperature, basified to pH 8 with saturated sodium bicarbonate, diluted with water (3 mL) and extracted with ethyl acetate (x3). The combined organic extract was washed with saturated brine, evaporated to dryness *in vacuo* and pumped to

constant weight to give the title compound (16 mg, 83%). Mp 147-150°C; MS(ES) m/e 399 $[M+H]^+$.

BIOLOGICAL DATA

Effect of Compounds on the CGRP Receptor

The test compounds were assayed for the inhibition of [^{125}I] CGRP (obtained from Amersham, Chicago, IL) binding and CGRP-activated adenylate cyclase activity.

SK-N-MC cells were obtained from American Type Culture Collection (Rockville, MD) and grown in Minimum Essential Media ("MEM") medium containing fetal calf serum (10%). Cells were grown in T-150 flasks or Costar multiwell plates (24 well) and maintained at 37 °C in a 90% humidified incubator with an atmosphere of 5% CO_2 and 95% air.

[^{125}I] CGRP Binding assay:

SK-N-MC cells were homogenized in 5 mM Tris-HCl pH 7.4, 10 mM Na-EDTA and the homogenate was centrifuged at 48,000 g for 20 min at 4 °C. The pellet was resuspended in 20 mM Na-HEPES pH 7.4, 10 mM $MgCl_2$ and recentrifuged as above. The membrane pellets were resuspended in the same buffer and stored frozen at -70 °C. The protein concentration was measured by the Pierce BCA method using bovine serum albumin as the standard.

The [^{125}I] CGRP receptor binding assay was performed using a buffer containing 20 mM Na-HEPES pH 7.4, 10 mM $MgCl_2$, 0.05% BSA and 0.1 mg/mL bacitracin. The membranes (50 ug protein/mL) were incubated with various concentrations (1, 10, 30, 60 and 100 uM) of the test compounds and 40 pM [^{125}I] CGRP in a total volume of 500 uL. for 60 min at 25 °C. The reaction was terminated by addition of 2 mL ice-cold 0.9% NaCl, followed by rapid filtration through Skatron Filtermates presoaked in 0.5% polyethylenimine PEI). The filters were rinsed twice with 2 mL of cold 0.9% NaCl and the radioactivity counted in a gamma counter. All binding data was analyzed by computer assisted LIGAND 2 program.

Adenylate cyclase activity:

Adenylate cyclase activity was measured in triplicate as the rate of conversion of α[^{32}P]ATP to [^{32}P]cAMP as previously described (Aiyer et al., *Endocrinology*, Vol. 129, pp. 965-969 (1991)). Human neuroblastoma cell (SK-N-MC) membranes [40-60 µg] were incubated in triplicate in buffer containing 50

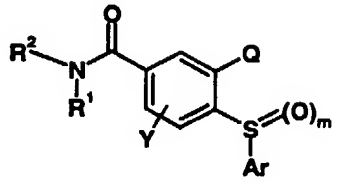
mM Tris-HCl (pH 7.4), 10 nM $MgCl_2$, 1.2 mM ATP, 1.0 μCi α[^{32}P]ATP, 0.1 mM cAMP, 2.8 nM phosphoenolpyruvate and 5.2 μg/ml myokinase in a final volume of 100 μl for 20 min at 30°C. The reactions were stopped with 1 ml solution containing cAMP, ATP and 22000 cpm of [^{3}H] cAMP. [^{32}P]cAMP was separated using sequential chromatography (Dowex and alumina columns) (Salmon et al., *Ana. Biochem.* Vol. 58, pp. 541-548 (1974)). Adenylate cyclase activities were determined in the absence (basal) or presence of 2.5 nM of hCGRPα with various concentrations (0.1 μM to 30 μM) of compound.

The compounds of this invention show CGRP receptor antagonist activity having IC_{50} values in the range of 0.001 to 100 μM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are ligands of the CGRP receptor and which bind thereto with an IC_{50} value in the range of 0.001 to 100 μM.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

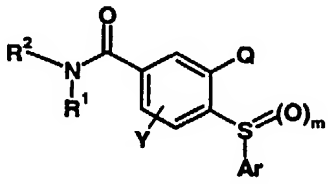
Q is NO_2 or NH_2;
Y is hydrogen, halo, CF_3, alkyl, alkoxy, NO_2, cyano;
R^1 is phenyl, substituted phenyl, heteroaryl, substituted heteroaryl;
R^2 is H, methyl, C_{2-4} alkyl, CH_2-A-$CONR^3R^4$, CH_2-A-CO_2R^5, CH_2-A-COR^5, CH_2-A-$SO_2NR^3R^4$, CH_2-A-$N(R^3)SO_2R^5$, CH_2-A-$N(R^3)COR^5$, CH_2-A-$N(R^3)CO_2R^6$, CH_2-A-$N(R^3)C(O)NR^3R^4$, CH_2-A-$N(R^3)C(O)NR^3SO_2R^5$, or CH_2-A-$OC(O)NR^3R^4$;
A is $(CH_2)_n$ where n is 0-6, or C_6H_4;
R^3 and R^4 independently are H, C_{1-6} alkyl, or C_{1-4} alkylphenyl, or R^3 and R^4, together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring;
R^5 is methyl, trifluoromethyl, C_{2-6} alkyl, phenyl, heteroaryl;
R^6 is tert-butyl, CH_2-phenyl, CH_2-pyridinyl;
m is 0, 1 or 2; and
Ar is phenyl, substituted phenyl, heteroaryl, substituted heteroaryl.

2. The compound as claimed in claim 1 selected from:
(±)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(+)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(-)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(±)-4-[(4-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(±)-N-methyl-N-(2-methylphenyl)-4-[(1-oxido-2-pyridinyl)sulfinyl]-3-nitrobenzamide;
(±)-N-methyl-N-(2-methylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide;

(±)-N-methyl-N-(2-methylphenyl)-4-[(5-methyl-1, 3, 4-thiadiazol-2-yl)sulfinyl]-3-nitrobenzamide; and
N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide.

3. A pharmaceutical composition comprising a compound of formula (I) according to claim 1 and a pharmaceutically acceptable carrier.

4. A method of treating a CGRP-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



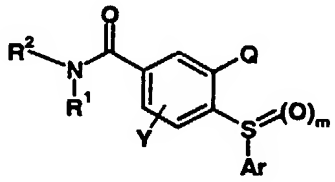
Formula (I)

wherein:
Q is NO_2 or NH_2;
Y is hydrogen, halo, CF_3, alkyl, alkoxy, NO_2, cyano;
R^1 is phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl;
R^2 is H, methyl, C_{2-4} alkyl, CH_2-A-$CONR^3R^4$, CH_2-A-CO_2R^5, CH_2-A-COR^5, CH_2-A-$SO_2NR^3R^4$, CH_2-A-$N(R^3)SO_2R^5$, CH_2-A-$N(R^3)COR^5$, CH_2-A-$N(R^3)CO_2R^6$, CH_2-A-$N(R^3)C(O)NR^3R^4$, CH_2-A-$N(R^3)C(O)NR^3SO_2R^5$, or CH_2-A-$OC(O)NR^3R^4$;
A is $(CH_2)_n$ where n is 0-6, or C_6H_4;
R^3 and R^4 independently are H, C_{1-6} alkyl, or C_{1-4} alkylphenyl, or R^3 and R^4, together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring such as piperidine, piperazine, or morpholine;
R^5 is methyl, trifluoromethyl, C_{2-6} alkyl, phenyl, or heteroaryl;
R^6 is tert-butyl, CH_2-phenyl, or CH_2-pyridinyl;
m is 0, 1 or 2; and
Ar is phenyl, substituted phenyl, heteroaryl, or substituted heteroaryl.

5. The method as claimed in claim 3 wherein the compound of formula (I) is a compound selected from:

(±)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(+)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(-)-4-[(2-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(±)-4-[(4-chlorophenyl)sulfinyl]-N-methyl-N-(2-methylphenyl)-3-nitrobenzamide;
(±)-N-methyl-N-(2-methylphenyl)-4-[(1-oxido-2-pyridinyl)sulfinyl]-3-nitrobenzamide;
(±)-N-methyl-N-(2-methylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide;
(±)-N-methyl-N-(2-methylphenyl)-4-[(5-methyl-1, 3, 4-thiadiazol-2-yl)sulfinyl]-3-nitrobenzamide; and
N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3-nitro-4-(2-thiazolylsulfinyl)benzamide.

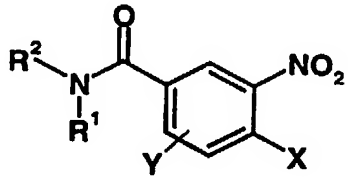
6. A process for preparing a compound defined in claim 1 having the structure of formula (I)



Formula (I)

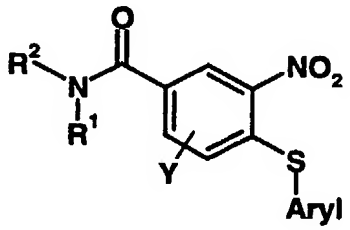
which comprises the steps of:

(a) reacting a suitable aryl thiol compound with a compound of formula (II)



Formula (II)

wherein, X is a suitable leaving group selected from halogen and NO_2, and R^1, R^2 and Y are defined in claim 1, in the presence of a base to provide a compound of formula (III)



Formula (III)

and

(b) oxidizing the compound of formula (III) with an appropriate oxidizing agent to provide a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12304

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 285/12, 211/12; C07C 323/14, 255/50, 317/10
US CL :548/136; 546/249; 564/162; 558/415; 560/11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/136; 546/249; 564/162; 558/415; 560/11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,602,084 A (HURTER) 22 July 1986, col. 1, lines 1-68, col. 2, 1-45.	2 and 5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 11 SEPTEMBER 1998	Date of mailing of the international search report 13 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EBENEZER SACKEY Telephone No. (703)-308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*